



# UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE  
United States Patent and Trademark Office  
Address: COMMISSIONER FOR PATENTS  
P.O. Box 1450  
Alexandria, Virginia 22313-1450  
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/888,326	06/22/2001	George Weiner	C1039/7052 (AWS)	7237

7590 05/29/2008  
Alan W. Steele  
Wolf, Greenfield & Sacks, P.C.  
Federal Reserve Plaza  
600 Atlantic Avenue  
Boston, MA 02210

EXAMINER
----------

ANGELL, JON E

ART UNIT	PAPER NUMBER
----------	--------------

1635

MAIL DATE	DELIVERY MODE
-----------	---------------

05/29/2008

PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b> 09/888,326	<b>Applicant(s)</b> WEINER ET AL.	
	<b>Examiner</b> J. E. Angell	<b>Art Unit</b> 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) ☒ Responsive to communication(s) filed on 11 February 2008.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) ☒ Claim(s) 1,8,9,11,14,15,17-21,24,34,43,56 and 78-104 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1,8,9,11,14,15,17-21,24,34,43,56,78-91,94-98 and 100-103 is/are rejected.
- 7) ☒ Claim(s) 92,93,99 and 104 is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 18 January 2002 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |  |  |
|--|--|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input checked="" type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)   | 5) <input type="checkbox"/> Notice of Informal Patent Application                                  |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date <u>11/8/2007</u> . | 6) <input type="checkbox"/> Other: _____   |

### **DETAILED ACTION**

This Action is in response to the communication filed on 2/11/2008.

The amendment filed 2/11/2008 is acknowledged and has been entered.

Claims 1, 8, 9, 11, 14, 15, 17-21, 24, 34, 43, 56, 78-104 are currently pending in the application and are addressed herein.

Applicant's arguments are addressed on a per section basis. The text of those sections of Title 35, U.S. Code not included in this Action can be found in a prior Office Action. Any rejections not reiterated in this action have been withdrawn as being obviated by the amendment of the claims and/or applicant's arguments.

### ***Information Disclosure Statement***

1. The information disclosure statement (IDS) submitted on 11/7/2007 is acknowledged. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

### ***Claim Rejections - 35 USC § 112***

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. Claims 1, 8, 9, 11, 14, 15, 17-21, 24, 34, 43, 56, 78-91, 94-98 and 100-103 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification

Art Unit: 1635

in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the claims encompass a method that comprises administering a nucleic acid comprising at least the formula 5' XI-X2-C-G-X3-X4 3', wherein C is unmethylated and wherein X1, X2, X3, and X4 are nucleotides, in an effective amount to upregulate expression of CD19, CD20 or CD22 surface antigen in B-cell malignancies. Therefore, the claims encompass a genus of oligonucleotides which upregulate expression of CD19, CD20 and CD22 in a malignant B-cell. It is noted that Applicants contend that the fact that an unmethylated CpG oligonucleotide upregulates CD19, CD20 and CD22 expression in B-cell malignancies is surprising and unexpected. For instance, page 11 (paragraph 0046 of the specification) states:

“The invention is based, in part, on the surprising discovery that administration to a subject of immunostimulatory nucleic acids induces the expression of cell surface antigens including CD20, CD19, and CD22 on the surface of a cancer cell and that the induction of these antigens leads to enhanced antibody-dependent cellular cytotoxicity (ADCC). It was previously believed that CpG oligonucleotides enhanced ADCC by influencing the effector cell (e.g., by activating natural killer (NK) cells). Now it has been discovered according to the invention that immunostimulatory nucleic acids actually cause the induction of specific antigens CD20, CD19, and CD22, each of which can be targeted by specific antibody therapies.”

The Examples disclosed in the specification only disclose one specific oligonucleotide, ODN 2006 (SEQ ID NO: 729) which has the ability to upregulate surface antigens CD19, CD20

Art Unit: 1635

and CD22 in malignant B-cell tumor cells. There is no indication that any other oligonucleotide was able to upregulate expression of a surface antigen in malignant B-cells. Considering that it was surprising and unexpected that SEQ ID NO: 729 was able to upregulate expression of CD19, CD20, and CD22 in B-cell malignancies, it is impossible to determine if any other oligonucleotide that meets the structural limitations of the claims would have the required activity without performing additional experimentation. Furthermore, since the control oligonucleotide was a poly-C oligonucleotide, it is impossible to tell if it is unmethylated CpG motif of ODN 2006 or some other aspect of the oligonucleotide which confers its surprising function.

Therefore, the specification does not contain a sufficient recitation of distinguishing identifying characteristics to provide adequate written description of the claimed genus.

*Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states, “applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of *the invention*. The invention is, for purposes of the ‘written description’ inquiry, *whatever is now claimed*.” (See page 1117.) The specification does not “clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed.” (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of molecules, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required.

Art Unit: 1635

See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

Therefore, only the oligonucleotide sequence that is SEQ ID NO: 729 meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

2. Claims 1, 8, 9, 11, 14, 15, 17-21, 24, 34, 43, 56, 78-91, 94-98 and 100-103 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

A method for inhibiting the growth of a B-cell malignancy, said method comprising administering to a subject having the B-cell malignancy:

a) administering an immunostimulatory nucleic acid sequence to the subject in an amount effective to upregulate expression of CD20, CD19 or CD22 surface antigen in cancer cells of the B-cell malignancy wherein the immunostimulatory nucleic acid sequence is SEQ ID NO: 729 and wherein the immunostimulatory nucleic acid sequence comprises an unmethylated CpG motif and wherein the nucleic acid sequence further comprises a backbone modification; and

b) an antibody specific for the surface antigen which is upregulated in response to administration of the immunostimulatory oligonucleotide; wherein administration of the immunostimulatory nucleic acid and the antibody results in the inhibition of the growth of the B-cell malignancy;

does not reasonably provide enablement for entire scope of the instant claims. For instance, the specification does NOT provide enablement for: (1) **preventing** cancer in subject a subject (as is encompassed by claim 56), and (2) using any oligonucleotide encompassed by the claims other than SEQ ID NO: 729 (as is encompassed by all of the instant claims). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988).

*Wands* states on page 1404,

“Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *Ex parte Forman*. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.”

The nature of the invention and breadth of the claims:

In their broadest embodiments (e.g., claim 56) the instant claims encompass a method of treating cancer comprising: administering to a subject (a) an immunostimulatory CpG oligonucleotide between 6 and 100 nucleotides long comprising a modified backbone and further comprising at least the formula 5' X<sub>1</sub>X<sub>2</sub>CGX<sub>3</sub>X<sub>4</sub> 3' wherein C is unmethylated and wherein X<sub>1</sub> X<sub>2</sub> X<sub>3</sub> and X<sub>4</sub> are nucleotides, in an amount effective to upregulate CD20, CD19 or CD 22 expression and b) and an antibody chosen from an anti-CD20 antibody, an anti-CD19 antibody and an anti-CD22 antibody in an effective amount to treat the cancer. Therefore, the general nature of the invention is cancer immunotherapy and encompasses administering a combination of an antibody and an immunostimulatory nucleic acid. Since claim 56 does not explicitly indicate that the subject has cancer, the claim encompasses “treating” a subject at risk of developing a B-cell malignancy (i.e., preventing a B-cell malignancy).

The unpredictability of the art and the state of the prior art:

Regarding the use immunostimulatory nucleic acids, the art recognizes a number of specific characteristics of the oligonucleotide which are critical for its function as an

Art Unit: 1635

immunostimulatory molecule. For instance, Krieg (BioDrugs, 1998; 5:341-346, previously of record) teaches,

“Synthetic oligonucleotides ranging in length from 8 to 30 nucleotides or more could cause immune stimulation if there was only a single CpG dinucleotide as long as this was not preceded by a C or followed by a G. Most importantly, the CpG dinucleotide had to be unmethylated: if the C was replaced by 5-methyl-cytosine, then the oligonucleotide lost its immune stimulatory activity.” (See p. 342, first paragraph).

Agrawal et al. (Trends in Mol. Med., 2002; 8:114-121, previously cited) teaches that sequences required for CpG related immune stimulation varies from species to species, and specifically indicates, “The optimal motif for recognition by human immune cells is GTCGTT or TTCGTT” (See p. 115, first paragraph). Thus indicating there is variability in the efficacy in the immunostimulatory oligonucleotides encompassed by the claims.

There is no teaching in the prior or post-filing art indicating that any cancer can be prevented without any chance of occurrence, thus indicating the high degree of unpredictability of preventing cancer. In fact, methods for curing/preventing cancer would encompass all of the problems associated with treating cancer, as well as additional obstacles such as preventing the events that lead to transformation of a normal cell into a cancer cell including preventing genetic mutation, and immortalization.

#### Working Examples and Guidance in the Specification

The specification has one working example specifically indicating that one specific unmethylated CpG oligonucleotide, ODN 2006 (SEQ ID NO: 729) had the ability to upregulate expression of CD19, CD20 and CD22 in malignant human B-cells (e.g., see Example 1). It is acknowledged that Example 3 indicates that the combination of ODN 1826 and a mouse IgG2a



Art Unit: 1635

monoclonal antibody (MS11G6) significantly improved survival of mice having tumors compared to control mice (see, pages 76-77). However, in view of the teaching of Agrawal et al. (indicated above) the result does not necessarily indicate that the ODN 1826 would have the same effect on human tumor cells. Furthermore, there is no evidence that ODN 1826 increased expression of CD19, CD20 or CD22 in the mice tumor cells. Additionally, there is no evidence that any oligonucleotide other than the unmethylated ODN 2006 upregulated expression of CD19, CD20 or CD22 in tumor cells.

Also, there are no examples or guidance indicating that B-cell malignancy can be prevented.

The data presented in the specification indicate that the discovery that an unmethylated CpG oligonucleotide can upregulate expression of CD19, CD20 and CD22 in tumor cells is “surprising”. It is accepted that this finding is surprising, and thus unexpected. However, considering that the result is unexpected, the specification only provides enablement for the disclosed protocol which confers the unexpected result. That is, since the results are unexpected, the only embodiments of the claims which the specification enables is a method for treating a subject having a B-cell malignancy comprising administering an immunostimulatory oligonucleotide that is ODN 2006 (SEQ ID NO: 729) wherein the oligonucleotide comprises an unmethylated CpG motif wherein the oligonucleotide is administered in an effective amount to upregulate expression CD19, CD20 or CD22 surface antigen in cells of said B-cell malignancy and further comprising administering an antibody that is specific for the surface antigen whose expression is upregulated.

#### Quantity of Experimentation

Art Unit: 1635

Considering the breadth of the claims and the limited working examples and guidance in the specification, one of skill in the art would be required to perform additional experimentation in order to be able to effectively use the invention to the full scope of the claims. For instance, considering the prior art teachings and the examples/guidance provided in the specification, additional experimentation would be required in order to use any immunostimulatory oligonucleotide other than an ODN 2006 comprising an unmethylated CpG motif and further comprising a backbone modification to upregulate expression of CD19, CD20 or CD22 in B-cell malignancies. Furthermore, additional experimentation would be required with respect to preventing a B-cell malignancy, as encompassed by claim 56.

Level of the skill in the art

The level of the skill in the art is deemed to be high.

Conclusion

Considering 1) the high degree of unpredictability of recognized in the art indicated above; 2) the breadth of the claims; 3) the limited working examples and guidance in the specification; and 4) the high degree of skill required, it is concluded that the amount of experimentation required to perform the broadly claimed to the full scope encompassed by the claims is undue.

***Response to Arguments***

3. Applicant's arguments filed 2/11/2008 have been fully considered.
4. With respect to the Rejection of claims under 35 USC 112, 1<sup>st</sup> paragraph (Written Description), Applicants argue that they have discovered and disclosed immunostimulatory

Art Unit: 1635

properties of nucleic acids that are defined by a common structural feature, a CpG motif.

Applicant asserts that the immunostimulatory nucleic acids are capable of upregulating cell surface antigens and when combined with an antibody against such cell surface antigens provide a means of treating disorders such as B-cell malignancies. Applicants refer to *In re Alton*, 76 F.3d 1168, 37 USPQ2d 1578 (Fed. Cir. 1996) in support of their argument. Applicants also distinguish the instant case from *Fiers v. Revel* and *Amgen Inc. v. Chugai Pharmaceuticals Co., Ltd.* Applicant contend that they have provided an adequate written description for the group of CpG immuno-stimulatory nucleic acids claimed.

In response, it is acknowledged that Applicants have disclosed a general formula for the CpG oligonucleotides encompassed by the claims. However, it is respectfully pointed out that the instant claims encompass only those CpG oligonucleotides of the given formula which effectively upregulate expression of CD19, CD20 and/or CD22 in malignant B-cells. Thus, the issue is not whether or not applicants have provided enough information on how to make every oligonucleotide encompassed by the given formula. The issue is whether or not the specification has provided sufficient guidance to show which of the CpG oligonucleotides encompassed by the given formula have the required function, which effectively upregulate expression of CD19, CD20 and/or CD22 in malignant B-cells. It is acknowledged that Applicants have provided evidence that a single CpG oligonucleotide of the given formula has the required function, that oligonucleotide being SEQ ID NO: 729. There is no evidence of record indicating that even one other CpG oligonucleotide of the given formula has the required function. Furthermore, as indicated above, the specification clearly indicates upregulation of CD19, CD20 and CD22 by the tested oligonucleotide was unexpected (see paragraph [0046]). Additionally, of one skill in

Art Unit: 1635

the art would recognize that different CpG oligonucleotides can have different effects (e.g., see references cited in the enablement rejection). Therefore, considering all of the evidence of record as a whole, the specification does not sufficiently describe the genus of CpG oligonucleotides encompassed by the claims (which must have the required function) to meet the written description requirement. With respect to *In re Alton*, it is respectfully pointed out that according to *In re Alton*, "One shows that one is 'in possession' of *the invention* by describing the *invention* with all its claimed limitations, not that which makes it obvious". In the instant case, Applicants have not adequately described the *invention with all its claim limitations* because (1) the evidence of record indicates that there is variability in the function of different CpG oligonucleotides, (2) the specification indicates that the results of the single experiment were unexpected and surprising, and (3) there is no guidance provided which indicates which CpG oligonucleotides of the given formula (other than SEQ ID NO: 729) would have the required function. With respect to *Amgen Inc. v. Chugai Pharmaceutical Co., Ltd.*, it is noted that the case concerned a patent that included claims to all possible DNA encoding sequences that have activity resembling that of the specific DNA sequence encoding the erythropoietin protein, but the Applicant had disclosed only a single specific DNA sequence of erythropoietin having a specific activity. Similarly, *Fiers v. Revel* concerned claims which purported to cover all DNAs that code for a specific human protein (human fibroblast beta-interferon). In the instant case, Applicants claims encompass all possible DNA molecules which meet the given formula and which have a required function, but Applicants have disclosed only a single specific DNA sequence having the required function. Therefore, although the fact patterns of the

Art Unit: 1635

particular decisions are different from the instant case, the decisions are relevant to the instant case.

With respect to the instant rejection of claims under 35 USC 112, 1<sup>st</sup> paragraph (Scope of Enablement), Applicants take issue with the references cited as indicating the state of the art. With respect to the Krieg reference, Applicants assert that Krieg is not in disagreement with the disclosure. With respect to the Agrawal reference, Applicants argue that Agrawal merely teaches that a particular motif was found to be the optimal motif which does not discount other oligonucleotides that do not contain the optimal motif. Applicants assert that a demonstration that molecules can be optimized is not evidence that the invention as a whole is not enabled. Applicants assert that there is no requirement that there is no requirement that Applicants provide a working example for each and every embodiment of the claims and refer to MPEP 2164.02. Applicants contend that no undue experimentation is required to practice the claimed method.

In response, with respect to the Krieg reference, it is reiterated that Krieg teaches,

“Synthetic oligonucleotides ranging in length from 8 to 30 nucleotides or more could cause immune stimulation if there was only a single CpG dinucleotide as long as this was not preceded by a C or followed by a G. Most importantly, the CpG dinucleotide had to be unmethylated: if the C was replaced by 5-methyl-cytosine, then the oligonucleotide lost its immune stimulatory activity.” (See p. 342, first paragraph).

In the instant case the given formula in the claims encompasses an oligonucleotide that is as small as 6 nucleotides and can comprise as little as a single CpG dinucleotide and there is no restriction barring the CpG dinucleotide from being preceded by a C or followed by a G. Thus, Krieg teach that particular members of the claimed genus would not cause immune stimulation. With respect to Agrawal, it is acknowledged that demonstration that molecules can be optimized is not evidence that the invention as a whole is not enabled. However, Agrawal does clearly

Art Unit: 1635

indicate that there is variability between different CpG oligonucleotides. That is, Agrawal teaches that different CpGs can have different effects. For instance, Agrawal teaches, “Recent studies have identified two structurally distinct CpG DNAs that activate human peripheral blood mononuclear cells (PBMCs) resulting in the production of different cytokines.” (See page 115, second column). This is important to the instant case because it shows that different CpG oligonucleotides can have different effects. Therefore, one can not predict that all CpG oligonucleotides will have the same effect. Furthermore, Agrawal also specifically teaches particular CpG motifs that do not stimulate an immune response, including CpG motifs encompassed by the claims. For instance, Agrawal teaches, “Recent studies also suggest that an accessible 5'-end of CpG DNA is required for immunostimulatory activity.” (See page 119, first column). Therefore, Agrawal provides more than a mere indication that the CpGs can be optimized. It is acknowledge that there is no requirement for a working example of each and every embodiment of the claim. It is also respectfully pointed that MPEP 2164.02 indicates, “To make a valid rejection, one must evaluate all the facts and evidence and state why one would not expect to be able to extrapolate that one example across the entire scope of the claims.” In the instant case all of the facts and evidence have been evaluated and it has been stated why one would not be able to extrapolate the one example across the entire scope of the claims, thus the instant rejection is proper. Furthermore, regarding a claimed genus, such as the instant case, it is respectfully pointed out that MPEP 2164.02 indicates, “The Federal Circuit has repeatedly held that 'the specification must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation'." *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).” Since the prior art of record clearly indicates that not

Art Unit: 1635

every CpG oligonucleotide will have the same effect and some CpG oligonucleotides do not function and in view of the fact that the specification has only provided a single working example for the entire genus of CpG oligonucleotides encompassed by the claims further experimentation would be required in order to enable the full scope of the claims. Considering that the claims encompass CpG oligonucleotides which the prior teaches would not stimulate an immune response and in view of the fact that the results of the single examples are “unexpected” and “surprising”, the amount of additional experimentation would constitute trial-and-error experimentation without guarantee of success. Furthermore, in view of the enormous number of different oligonucleotides that meet the structural limitation of the claims (i.e., all nucleotide sequences 6 to 100 nucleotides in length which comprise a CG motif wherein the C is unmethylated), the additional experimentation that is required is considered undue.

Therefore, Applicants arguments as they pertain to the pending rejections are not persuasive.

### ***Claim Objections***

5. Claims 92, 93, 99 and 104 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

### ***Conclusion***

6. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. E. Angell whose telephone number is 571-272-0756. The examiner can normally be reached on Monday-Thursday 8:00 a.m.-6:00 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Douglas Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/J. E. Angell/  
Primary Examiner, Art Unit 1635